Safety of live vaccinations on immunosuppressive therapy in patients with immune-mediated inflammatory diseases, solid organ transplantation or after bone-marrow transplantation - A systematic review of randomized trials, observational studies and case reports

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Abstract: BACKGROUND: Live vaccines are generally contraindicated on immunosuppressive therapy due to safety concerns. However, data are limited to corroborate this practice. OBJECTIVES: To estimate the safety of live vaccinations in patients with immune-mediated inflammatory diseases (IMID) or solid organ transplantation (SOT) on immunosuppressive treatment and in patients after bone-marrow transplantation (BMT). DATA SOURCES: A search was conducted in electronic databases (Cochrane, Pubmed, Embase) and additional literature was identified by targeted searches. ELIGIBILITY CRITERIA: Randomized trials, observational studies and case reports. POPULATION: Patients with IMID or SOT on immunosuppressive treatment and BMT patients <2years after transplantation. INTERVENTION/VACCINATIONS LOOKED AT Live vaccinations: mumps, measles, rubella (MMR), yellow fever (YF), varicella vaccine (VV), herpes zoster (HZ), oral typhoid, oral polio, rotavirus, Bacillus Calmette-Guérin (BCG), smallpox. DATA EXTRACTION: One author performed the data extraction using predefined data fields. It was cross-checked by two other authors. RESULTS: 7305 articles were identified and 64 articles were included: 40 on IMID, 16 on SOT and 8 on BMT patients. In most studies, the administration of live vaccines was safe. However, some serious vaccine-related adverse events occurred. 32 participants developed an infection with the vaccine strain; in most cases the infection was mild. However, in two patients fatal infections were reported: a patient with RA/SLE overlap who started MTX/dexamethasone treatment four days after the YFV developed a yellow fever vaccine-associated viscerotropic disease (YEL-AVD) and died. The particular vaccine lot was found to be associated with a more than 20 times risk of YEL-AVD. One infant whose mother was under infliximab treatment during pregnancy received the BCG vaccine at the age of three months and developed disseminated BCG infection and died. An immunogenicity assessment was performed in 43 studies. In most cases the patients developed satisfactory seroprotection rates. In the IMID group, YFV and VV demonstrated high seroconversion rates. MTX and tumor necrosis factor inhibitory therapy appeared to reduce immune responses to VV and HZ vaccine, but not to MMR and YF-revaccination. Seroconversion in SOT and BMT patients showed mostly higher rates for rubella than for measles, mumps and varicella. LIMITATIONS: Risk of bias was high in the majority of studies since 39 of them were observational and 17 were case series/case reports. Only eight studies were randomized trials. BMT patient numbers included in this review were low. CONCLUSIONS: Although live vaccinations were safe and sufficiently immunogenic in most studies, some serious reactions and vaccine-related infections were reported in immunosuppressed IMID and SOT patients. Apart from mild vaccine-related infections MMR and VV vaccines were safe when administered less than two years after BMT. IMPLICATIONS OF KEY FINDINGS: Until further data are available, live vaccinations under most immunosuppressive treatments should only be administered after a careful risk benefit assessment of medications and dosages. FUNDING: None.

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Title

Safety of live vaccinations on immunosuppressive therapy in patients with immune-mediated inflammatory diseases, solid organ transplantation or after bone-marrow transplantation – a systematic review of randomized trials, observational studies and case reports

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Abstract

Background: Live vaccines are generally contraindicated on immunosuppressive therapy due to safety concerns. However, data are limited to corroborate this practice.

Objectives: To estimate the safety of live vaccinations in patients with immune-mediated inflammatory diseases (IMID) or solid organ transplantation (SOT) on immunosuppressive treatment and in patients after bone-marrow transplantation (BMT).

Data Sources: A search was conducted in electronic databases (Cochrane, Pubmed, Embase) and additional literature was identified by targeted searches.

Eligibility criteria: Randomized trials, observational studies and case reports.

Population: Patients with IMID or SOT on immunosuppressive treatment and BMT patients <2 years after transplantation.

Intervention/vaccinations looked at: Live vaccinations: mumps, measles, rubella (MMR), yellow fever (YF), varicella vaccine (VV), herpes zoster (HZ), oral typhoid, oral polio, rotavirus, Bacillus Calmette–Guérin (BCG), smallpox.

Data extraction: One author performed the data extraction using predefined data fields. It was cross-checked by two other authors.

Results: 7,305 articles were identified and 64 articles were included: 40 on IMID, 16 on SOT and 8 on BMT patients. In most studies, the administration of live vaccines was safe. However, some serious vaccine-related adverse events occurred. 32 participants developed an infection with the vaccine strain; in most cases the infection was mild. However, in two patients fatal infections were reported: a patient with RA/SLE overlap who started MTX/dexamethasone tretament four days after the YFV developed a yellow fever vaccine-associated viscerotropic disease (YEL-AVD) and died. The particular vaccine lot was found to be associated with a more than 20 times risk of YEL-AVD. One infant whose mother was under infliximab treatment during pregnancy received the BCG vaccine at the age of three months and developed disseminated BCG infection and died. An immunogenicity assessment

was performed in 43 studies. In most cases the patients developed satisfactory seroprotection rates. In the IMID group, YFV and VV demonstrated high seroconversion rates. MTX and tumor necrosis factor inhibitory therapy appeared to reduce immune responses to VV and HZ vaccine, but not to MMR and YF-revaccination. Seroconversion in SOT and BMT patients showed mostly higher rates for rubella than for measles, mumps and varicella.

Limitations: Risk of bias was high in the majority of studies since 39 of them were observational and 17 were case series/case reports. Only eight studies were randomized trials. BMT patient numbers included in this review were low.

Conclusions: Although live vaccinations were safe and sufficiently immunogenic in most studies, some serious reactions and vaccine-related infections were reported in immunosuppressed IMID and SOT patients. Apart from mild vaccine-related infections MMR and VV vaccines were safe when administered less than two years after BMT.

Implications of key findings: Until further data are available, live vaccinations under most immunosuppressive treatments should only be administered after a careful risk benefit assessment of medications and dosages.

Funding: None.

Keywords

Immunosuppressive medication, live vaccine, immune-mediated inflammatory disease, solid organ transplantation, bone-marrow transplantation

Abbreviations

AEs – adverse events, BCG - Bacillus Calmette–Guérin, BMT - bone marrow transplantation, CSA - cyclosporine A, GvHD – graft versus host disease, HZ - herpes zoster, HZV - herpes zoster vaccine, IBD - inflammatory bowel disease, IFX – infliximab, IMID - immune-mediated inflammatory disease, INF – interferon, IVIG – intravenous immunoglobulin, JIA - juvenile idiopathic arthritis, MMF - mycophenolate-mofetil, MMR - mumps; measles; rubella, MS – multiple sclerosis, MTX – methotrexate, RA – rheumatoid arthritis, RCT – randomized controlled trial, RTX – rituximab, SAE – serious adverse event, SLE – systemic lupus erythematosus, SOT – solid organ transplantation, TAC – tacrolimus, TCZ – tocilizumab, TNFi – tumor necrosis factor inhibitor, VV – varicella vaccine, VZV – varicella zoster virus, YEL-AVD - yellow fever vaccine-associated viscerotropic disease, YF – yellow fever, YFV – yellow fever vaccine

Introduction

Immunizations are an important means for preventing infectious diseases in healthy individuals and especially in vulnerable patient groups with immunocompromising conditions. However, live vaccinations contain an attenuated vaccine strain, which has the theoretical potential to revert to the original pathogenic form and to induce infection by the vaccine strain, particularly in immunocompromised individuals. Serious infections with the vaccine strain and even deaths have occurred in HIV patients, leukemia patients and patients with inherited immunodeficiencies [1–4].

The number of individuals treated with immunosuppressive medications due to immune-mediated inflammatory diseases (IMID), solid organ transplantation (SOT) or patients after bone-marrow transplantation (BMT) has grown over the last decades [5]. Clinicians are increasingly exposed to the dilemma on whether an immunosuppressed patient can receive a live vaccine – which is very important as severe infections with infections preventable by live vaccinations such as measles and varicella can occur on immunosuppressive therapy [6,7]. On the other hand, the live vaccine itself may impose a danger to the immunosuppressed individual. Furthermore, vaccines may be less effective when administered to an impaired immune system [8].

To date, live vaccines are contraindicated under most immunosuppressive therapies. However, data are generally scarce. Over the last few years efforts have been made to evaluate the safety of some live vaccines in selected immunosuppressed individuals by conducting both, retrospective and prospective studies. Further data have become available as live vaccines were occasionally administered inadvertently or after a careful risk-benefit assessment to individual patients.

In this systematic review, we aim to provide an overview on the results of published randomized trials, observational studies and case reports on live vaccinations in patients with IMIDs or SOT on immunosuppressive therapy as well as BMT patients who received a live vaccine less than two years after receiving the BMT. Live vaccines are generally accepted after this 2 year time period in BMT

patients if no immunosuppressive therapy is given and no GvHD is present [9]. Our **primary objective** is to examine the **safety** of the live vaccinations (mumps, measles, rubella (MMR), yellow fever (YF), varicella vaccine (VV), herpes zoster (HZ), oral typhoid, oral polio, rotavirus, Bacillus Calmette–Guérin (BCG), smallpox) in patients on immunosuppressive treatment with an IMID or SOT as well as patients less than two years after BMT. This includes the assessment (i) of systemic or local vaccine reactions (ii) of the risk of infection with the attenuated vaccine strain, and (iii) on whether live vaccinations are associated with relapses/worsening of the underlying disease or organ rejection. Our **secondary objectives** are to examine the **immunogenicity** and the **clinical protection** of live vaccinations in these patients.

Methods

Eligibility criteria for study inclusion

Population: Patients of any age with an IMID or SOT who were on immunosuppressive treatment at the time of vaccination as well as patients less than two years after BMT were considered. As live vaccines are generally accepted two years after BMT if no immunosuppressive therapy is given and no GvHD is present publications on live vaccines more than two years after BMT were not considered.

Studied Vaccinations: Live attenuated vaccinations (MMR, YF, VV, HZ, oral typhoid, oral polio, rotavirus, BCG, smallpox).

Outcomes: Our primary outcome measure is the safety of live vaccinations; this includes the assessment (i) of systemic or local vaccine reactions (ii) of the risk of infection with the attenuated vaccine strain, and (iii) on whether live vaccinations are associated with relapses/worsening of the underlying disease or organ rejection. The secondary outcome measures are the immunogenicity and clinical protection of live vaccinations in patients with the conditions defined above. To assess immunogenicity we included humoral immune responses (antibody concentrations, seroconversion rates) and cellular responses, depending on the available information in the studies. As often no control group was studied we focused on clinical protection and not on efficacy or effectiveness of vaccinations.

Included Study Designs: Randomized trials, observational studies and case reports.

Information Sources

The Cochrane, Pubmed, Embase databases were searched without applying time restrictions. Unpublished (grey) literature (unpublished reports, conference abstracts) was retrieved through targeted website searches of relevant organizations and international conferences dealing with vaccination, infectious diseases, IMIDs, SOT and BMT, i.e. European League Against Rheumatism,

Centers for Disease Control and Prevention, Infectious Diseases Society of America, American College of Rheumatology, European Society for Organ Transplantation, American Society of Transplantation, European Society for Blood and Marrow Transplantation, American Society for Bone Marrow Transplantation. Additional articles were identified through reference lists of selected papers. The search was run on March 23rd 2014. A limited update search was run on January 22nd 2016.

Search terms were peer reviewed during the development process. The search terms in Figure 1 were used in combination to search the databases. Corresponding Medical Subject Headings and Embase subject headings were searched for.

Study selection

Two review authors performed eligibility assessment based on titles, key words, and abstracts independently (SB and VKJ). Disagreements between review authors were resolved by consensus. One review author conducted the eligibility assessment (EC) based on the full article; this was checked by two other review authors (SB and VKJ). If authors published several studies on the same subject (e.g. varicella vaccination in stem cell transplantation) we compared sample sizes, outcomes and time frames of study conduct to avoid double counting.

Data collection process

A data extraction sheet was piloted on five randomly-selected studies and was refined accordingly. Data extraction was performed by one author (EC) and checked by two other authors (SB and VKJ). In case of disagreement, a consensus was sought by discussion between the three authors. In 10 cases, study authors were contacted to receive further/clarifying information. Seven authors answered and in six cases the relevant information could be retrieved. In three cases the author did not respond and it could not be clarified whether the patients were treated with immunosuppressive therapy during the immunization. These three articles were excluded.

Data items

Information from each record was extracted on year of publication, year of study conduct, country, study design, number of participants, enrolment of controls, number of vaccine doses, underlying disease, immunosuppressive medication, primary vaccine dose or secondary/revaccination vaccine doses, vaccine reaction (local or systemic), infection through vaccine strain, flare of underlying disease (IMID) or transplant rejection (SOT/BMT), immunogenicity assessment performed, test for immunogenicity assessment, time point for immunogenicity assessment, results of immunogenicity assessment**,** clinical protection assessment performed, duration of follow-up for clinical protection, results of clinical protection assessment, conclusion (see supplementary file). If a live vaccine was administered to a seronegative patient it was defined as a "primary vaccination". If a second vaccination was given or if patients were known to be seropositive at the time of vaccination, the vaccination was defined as "secondary vaccination" or "re-immunization".

Results

Study selection

7,290 articles were identified through database searching and 15 articles were identified through other sources. After removal of duplicates, 7,187 articles remained. 550 articles were left after title and keyword screening and 105 (IMID n=64, BMT n=20, SOT n=21) articles were left after abstract screening (Figure 2). The full-text of these articles were assessed for eligibility and finally 64 articles were included in this systematic review (see supplementary file for details on included studies).

Of these, 40 (YF n=9 (n=8 in adults, n=1 in children and adults), MMR n=6 (n=1 in adults, n=5 in children), varicella n=12 (n=3 in adults, n=9 in children, n=1 in children and adults), HZ n=8 (all in adults), polio n=1 (adult), BCG n=4 (n=2 in adults, n=2 in children), live typhoid n=1 (adult), smallpox n=1 (adult)) were conducted in IMID patients. 16 studies (YF n=2 (n=1 in adults, n=1 in children and adults), MMR n=7 (all in children), varicella n=11 (n=2 in adults, n=9 in children), BCG n=1 (children)) were identified in SOT patients and eight (MMR n=4 (n=2 in children, n=2 in children and adults), varicella n=5 (n=1 in adults, n=2 in children, n=2 in children and adults)) in BMT patients. Some studies evaluated several live vaccines. No study on rotavirus vaccination was identified. In one study the participants (IMID patients) were vaccinated simultaneously against YF, MMR and varicella. In five studies (SOT patients) the participants were vaccinated against MMR and varicella simultaneously. 41 full-text articles were excluded because patients were not on immunosuppressive therapy at time point of vaccination (IMID or SOT, n=15), administration of live vaccine later than two years after BMT (n=11), no original work (n=12), the results were already presented in other articles (n=2), or because of an additional inherited immunodeficiency of the vaccinated patient (n=1). Out of the 64 included articles, eight were randomized controlled trials (RCTs), 39 observational studies and 17 case series/reports. RCTs were only identified in the IMID group (varicella n=5, HZ n=1, YF n=1, MMR n=1).

Study characteristics

A total of 21,082 patients received a live vaccine in the studies, which were published between 1977 and 2016. Studies were conducted in 18 different countries including USA (n=18), Brazil (n=13), Japan (n=6) and Germany (n=4). As some patients received several live vaccines concomitantly the presented numbers may not add up.

Immune mediated inflammatory diseases

Most of the patients (n=20,556) had an **IMID**. Of these, 19,630 patients received an HZ, 474 an MMR, 233 a YF, 202 a varicella, 10 an oral typhoid, 5 a BCG, one a live poliomyelitis and one a smallpox vaccination.

The most frequently represented disease categories in the IMID group are summarized in Table 1. The participants in the IMID group were under 22 different immunosuppressive medications. The most common medication in this group was glucocorticoids (n=384) with a prednisone-equivalent dosage range of 2.5-35mg/day, followed by methotrexate (MTX, n=268) with a dosage range of 5-27mg/m2/week. 98 patients in the IMID group were treated with a combination therapy; 218 received a monotherapy with a biological, 39 received a combination therapy with a biological. 633 patients received herpes zoster vaccine (HZV) under biological therapy. It was unclear whether this was a mono- or a combination therapy. In this study the medication was only reported in 7,780/18,683 patients. So numbers of patients with HZV on immunosuppressive therapy may have been higher [10]. In the IMID group, in 18 studies primary vaccinations were administered, in 13 studies secondary doses were given. In six studies a primary and a secondary vaccination were administered and in three studies it was unknown whether a primary or a secondary vaccination was given.

SOT

339 **SOT patients** with live vaccinations were identified; 192 were vaccinated against varicella, 172 against MMR, 20 against YF, and 24 received the BCG vaccine.

Of the 339 SOTs, 271 were liver transplants, 62 kidney transplants, four heart transplants, one small bowel transplant, and one liver and small bowel transplant. The SOT patients were treated with eight different immunosuppressive medications. The most frequently used medication was tacrolimus (TAC, n=134, 2.4-10ng/ml in serum), followed by cyclosporine A (CSA, n=56) with a dosage range from 30-120ug/l; 70 transplanted participants were under a combination therapy. In seven studies patients received a primary vaccination, in one study only revaccinations were given and in eight studies the patients received a primary vaccination as well as a secondary vaccination.

BMT

Only a small part of the participants were **patients with BMT (n=187).** Of these, 152 received an MMR vaccination and 38 received a VV. The underlying diseases of BMT patients are specified in Table 2. All BMT patients (n=38) who received VV, were not on current immunosuppressive therapy. 27 patients who received an MMR immunization were treated with an immunosuppressive therapy at vaccination (CSA n=12, CSA/prednisone n=11; prednisone n=2, mycophenolate-mofetil (MMF) n=2). In one study, seven BMT patients (MMR vaccination n=7, VV n=3) took a calcineurin inhibitor and MMF as graft versus host disease (GvHD) prophylaxis [11]. In five studies only primary vaccinations were administered and in three studies the patients received a primary and a secondary immunization.

Results of individual studies

Safety

Local or systemic vaccine reactions

Out of the 21,082 involved participants, local or systemic vaccine-associated adverse reactions were observed in 280 patients (1.3%): 207/20,556 (1.0%) in the IMID group, 61/339 (18.0%) in the SOT group and 12/187 in the BMT group (6.4%). Most frequent adverse reactions (n=269) were mild such as injection-site pain, headache, fatigue, myalgia, fever, arthralgia, and nausea. Serious adverse

events (SAEs) were reported by 11 participants (Table 3).

In one study SAEs were reported in 11 IMID patients under prednisone treatment who received HZV [12]. However, SAEs in the placebo group were as frequent as in the HZ-vaccinated group (6.6% *vs.* 5.7%). One of the SAEs in the HZ group was vaccine-related but the exact reason was not mentioned. Six deaths occurred (three in placebo group and three in HZ group), of which none was judged to be vaccine-related. The most frequently reported SAEs were respiratory, thoracic and mediastinal disorders [12].

After receiving MMR, poliomyelitis, small pox, live typhoid and BCG vaccination in the IMID group, there were no reported SAEs. Similarly, in the SOT and BMT group no SAEs were reported. Across IMID, SOT and BMT patients, 17 articles did not document whether adverse events were observed.

Pathology through unrestricted proliferation of the attenuated strain

32 participants developed an infection through the vaccine strain. Overall, one infection occurred after YFV, three after MMR vaccination, 20 after VV, five after HZV, one after live polio, one after BCG, and one after smallpox vaccination.

IMID

In 12 of 20,556 (0.06%) IMID patients a vaccine-strain-related infection was reported (Table 3). One 49-year old female patient with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) who started MTX and dexamethasone (dosage unknown) four days after the YFV developed a yellow fever vaccine-associated viscerotropic disease (YEL-AVD) and died [13,14]. She received the vaccination during a YF vaccination campaign in Peru, during which one particular vaccine lot was found to be associated with a more than 20 times risk of YEL-AVD. Among 42,742 persons who received a vaccine from this lot, five developed a YEL-AVD.

One juvenile idiopathic arthritis (JIA) patient with MTX experienced a rash and fever 20 days after a

primary MMR vaccination [15]. However, the rash was interpreted as disease-related [personal communication with authors].

One patient with muco-cutaneous lymphnode syndrome under steroid therapy developed mild varicella 11 days after immunization with VV [16], one SLE patient experienced a localized rash (<5 vesicles) after VV [17].

HZ and varicella zoster virus (VZV)-like rashes were seen in five patients after immunization with a HZV [10,12,18]. One of them experienced a serious ophthalmic herpes zoster infection which was determined to be vaccine-related by the investigator; however wild type virus and not vaccine strain virus was identified by PCR [12]. Another patient who received a 15-day supply of prednisone two months before being vaccinated, developed HZ seven days after vaccination [18]. One patient with reactive arthritis under 50mg etanercept had a positive stool culture for poliovirus Sabin 1-like RNA but without any symptoms after oral polio vaccination [19]. One infant whose mother was under infliximab (IFX) treatment during pregnancy received the BCG vaccine at the age of three months and developed disseminated BCG infection and died [20]. One patient with atopic eczema under topical fluocinolone or betamethasone therapy developed smallpox-like vesicles after the smallpox immunization and improved rapidly after receiving hyperimmune serum against vaccinia [21].

SOT

16/339 (4.7%) SOT patients had a vaccine-related infection (Table 3); 14 patients developed varicella after VV within two to eight weeks. In all 14 patients it was only a moderate form of varicella without complications [22–24]. Two patients had transient swelling of the parotid glands after mumps immunization [25,26].

BMT

In the BMT group one patient developed HZ seven days after receiving the varicella vaccine (Table 3) [27]. Symptoms resolved with treatment. In another study three patients developed a disseminated rash within 2.5 weeks after VV [28]. The rash resolved without treatment. In all four cases there was

not clear whether the reaction had occurred in patients vaccinated less than or more than two years after BMT.

Flare of underlying disease/ transplant rejection after vaccination

IMID

In a self-controlled case-series study, a 12.8 times (95%CI 4.28-38.13, p<0.001) higher exacerbation rate was reported in multiple sclerosis (MS) patients who received YFV under glatiramer acetate and interferon treatment compared to time periods when these patients had not received YFV ("not-at-risk-periods") [29]. In a retrospective cohort study by Heijstek et al [30], no aggravation of disease was registered in the MMR vaccinated JIA patients. In another study by Heijstek and colleagues [31], the mean number of flares per patient did also not differ significantly between the vaccinated patients and the control group. A boy with atopic dermatitis experienced an exacerbation of the skin disease one week after BCG vaccination [32]. The exacerbation of the skin lesions resolved 3.5 months later after treatment. While 1/10 patients with inflammatory bowel disease (IBD) under prednisolone 10mg had a flare 15 days after live typhoid immunization, 8/10 patients reported improvement of abdominal symptoms after 90 days [33]. In three further studies improvement of the basic diseases were reported. Two randomized controlled studies mentioned a significant improvement of the psoriatic area in 83% of psoriasis patients after four doses of VV [34,35]. Less patients in the control group showed a significant improvement. In a case report, two SLE patients experienced improvement of their extrarenal manifestations after BCG vaccination [36].

SOT

In the SOT group, three cases of organ rejections were reported. One patient developed an episode of acute rejection three weeks after measles vaccination. The other patient showed chronic rejection at the time of vaccination and remained unchanged for one year [37]. Another single rejection episode of the liver was reported, which occurred more than one year after a VV and was considered as unassociated to immunization [38].

BMT

One child after autologous BMT had a relapse of her malignancy after MMR immunization, the time point was unknown [39].

Immunogenicity

In 43 studies an immunogenicity assessment was performed: 23 (YF n=6, MMR n=3, VV n=9, HZ n=5) in the IMID group, 12 (YF n=1, MMR n=7, VV n=4) in the SOT group and in all eight studies (MMR n=3, VV n=5) in the BMT group. In the majority, an immunogenicity assessment was performed before vaccination; the time points for the immunogenicity assessment varied from 15 days to 13 years after vaccination.

IMID

In 19 articles the humoral immune response and in two articles the humoral and cellular response was assessed. In two articles the test method was not documented.

YF-vaccinated IMID patients showed high seroconversion rates in four articles, which did not differ between patients and controls [29,40–42]. Patients under therapy with short-term high dose corticosteroids, long-term low-dose corticosteroids, glatiramer acetate, interferon gamma (INF-y) or MTX received a primary YFV. Only in one of these studies, patients who received transcutaneous vaccination instead of subcutaneous vaccination demonstrated significantly lower YFV-specific T-cell responses [40]. After YF revaccination under IFX (±MTX), 1/17 patients and 1/15 controls remained seronegative [8]. In another study on rheumatic patients under various treatments a seropositivity of 87% was achieved after YF revaccination. Patients showed lower titers of neutralizing antibodies than healthy individuals [43]. The patient with the lowest antibody titer had been administered 2mg rituximab (RTX) four months before YF revaccination.

In one study, MMR-vaccinated JIA patients treated with low-dose MTX had lower levels of virus-specific antibodies and IFN-y producing T memory cells than healthy children [44]. The patients who

additionally received etanercept showed a decline of virus-specific IFN-y producing T cells and IgG antibodies were slightly increased. Kawasaki patients vaccinated against MMR within six months after administration of intravenous immunoglobulin (IVIG) had lower IgG concentrations against measles, mumps and rubella compared to controls [45]. Patients vaccinated later than nine months after IVIG administration did not show any difference to controls. No significant differences in humoral responses were observed between patients with and without MTX or biologics after MMR vaccination [31].

In three studies with a limited sample size, VV showed good immunogenicity results in IMID patients [16,46,47]. In two studies, SLE patients developed comparable VZV-specific antibody levels to controls [17,48]. However the cellular responses were lower in SLE patients [17].

In three studies JIA showed lower seroconversion rates than controls [49–51]. In one study all 10 non-converters were under sole MTX therapy or received additional prednisone [49]. In another study all four non-converters were under tumor necrosis factor inhibitor (TNFi) therapy [49]. In contrary to tocilizumab (TCZ) treated patients, patients under IFX/MTX and etanercept had insufficient responses [51]. In a report of six cases under treatment with mesalamine, olsalazine, 6-mercaptopurine, and/or IFX extremely varying results were observed [52].

In three studies HZV showed a worse immune response in immunosuppressed patients than in the immunocompetent group [53–55]. In a case report a patient with MS under fingolimod remained seronegative after administration of HZV, even despite he had two clinical episodes of HZ infection [54].

In a study 10 SLE patients under prednisone, hydroxychloroquine or MTX showed similar cellular immune responses as controls, but the increase of antibody levels was lower [55]. In two studies patients under treatment with steroids and further modifying agents achieved adequate antibody levels after HZV [12,56].

SOT

In 10 studies the humoral and in two studies cellular and humoral tests were performed. A kidney transplant recipient under CSA and mycophenolic acid vaccinated against YFV 19 years post-transplant reached antibody titers within the lower range of those of controls [57].

The seroconversion after post-transplant vaccination showed generally higher rates for rubella (range 70-100%) than for measles (44-100%), mumps (48-100%) and varicella (71%) [25,26,37,58–61]. Patients were under various therapies including CSA, prednisone, azathioprine and TAC. In two studies, the patients were also tested after a second or a third vaccination and showed higher seroconversion rates afterwards [58,59].

The seroconversion rate after VV in SOT patients varied from 25 to 87% [22,25,26,58–60,62,63]. In a study with patients under triple therapy with prednisone, CSA and azathioprine, 59% developed anti-varicella antibodies within the first four to eight weeks after a primary vaccine dose [62]. By three to six months after immunization, 85% were seropositive and at 24 months 76% of the antibody titers remained positive. In two studies, patients under MMF, prednisone, CSA, TAC or sirolimus reached similar seroconversion rates of 64-67% [60,63]. 87% of patients under CSA and TAC receiving one dose of VV seroconverted and 86% had positive cellular responses [22].

Patients under TAC and CSA receiving a varicella revaccination one year after liver transplantation, had seroconversion rates between 50% and 81% after re-immunization [26,58,59].

In a study all children (100%) reached seroconversion after one, two or three vaccinations [38]. After the last vaccine dose 96.8% (31/32) of the children retained high-median antibody titers. In 20 patients, VZV-specific CD4+ T cell responses were compared pre- and post- immunization and they showed a significant increase.

BMT

In four studies an immunogenicity assessment was performed by humoral tests, in one study by

cellular tests and in one study by humoral and cellular tests. In two BMT studies the test was unspecified.

Three studies with patients who received an MMR immunization within 24 months after BMT showed a higher seroconversion rate for rubella (86-100%) than for measles (33-46%) and mumps (29-80%) [11,39,64]. It was observed that children seroconverted more frequently to measles if they were immunized more than 15 months after BMT (35% prior to versus 78% after 15 months) [64]. Seroconversion rates were 86% for rubella, 43% for measles and 29% for mumps in patients treated with calcineurin inhibitors and MMF after a primary MMR vaccine [11].

In another study, after a primary measles vaccine dose, all patients seroconverted and 78% remained seropositive for at least 12 months [65]. However, only 44% of these patients were on immunosuppressive drugs at the time of vaccination.

For varicella vaccination after BMT, seroconversion rates varied between 33 and 89% after a primary VV [11,27,66,67]. In the study in which only 33% seroconversion was achieved, patients were under GvHD-prophylaxis with calcineurin inhibitors and MMF. In the other studies patients were without immunosuppressive treatment.

Clinical protection of vaccines

In the IMID group, 12/202 patients (6%) who received a VV nevertheless developed a varicella infection or HZ. 8/19,630 patients (0.04%) receiving a HZV later had a HZ infection despite vaccination. YF-, MMR-, Polio, BCG- and typhoid fever-vaccinated patients appeared to be protected and did not develop an infection.

In the SOT group, 7/192 (3.6%) patients developed a varicella infection despite being vaccinated against varicella. 2/38 (5.3%) in the BMT group developed varicella in spite of a VV. Patients in the SOT and BMT group who were vaccinated against YF, MMR and BCG were protected against infection. Follow-up periods for clinical protection varied between 6 weeks to 12.5 years.

Discussion

Whether live vaccines can be administered to immunocompromised patients is an often-encountered problem by physicians caring for this specific patient group. On the one hand these patients are especially vulnerable from infections (many of them vaccine-preventable) on the other hand there is a potential risk of harming the patient by the administration of a vaccine containing an attenuated vaccine strain, which has the theoretical potential to revert to the original pathogenic form and to induce infection in the immunocompromised individual. Apart from infecting the immunocompromised person, more vaccine-related side effects as well as re-activation of the underlying disease is feared. Therefore this review summarizes available information in order to inform the practitioner of currently available evidence by reviewing and giving an overview on currently available literature on this topic.

Generally local and systemic reactions were mild. While they were rare in IMID patients (prevalence of 1%), they occurred more frequently in BMT (6%) and SOT patients (18%). The percentages of adverse events (AEs) appear low compared to AEs reported in the general population [68–71]. This is most likely due to underreporting of AEs in our included studies.

Altogether, 11 SAEs due to local or systemic reactions including three deaths were reported; however, none of the deaths was vaccine-associated. All reported SAEs occurred in IMID patients after HZV. In the other vaccination groups, numbers of patients were low, thus SAEs may not have been observed due to the limited sample sizes. Also in the literature local or systemic SAEs after live vaccinations are extremely rare. For examples, anaphylactic reactions after YFV occur in 0.8-1.8/100,000 administered doses and thrombocytopenia after MMR vaccination is estimated to occur in one out of 30,000-40,000 administered MMR doses [72,73].

In the 2010 published recommendations on YFV on immunization practices of the Centers for Disease Control and Prevention report on several YEL-AVD cases in individuals with underlying autoimmune conditions: three patients with SLE, two with Addison's disease, one with Crohn's disease, one with

polymyalgia rheumatica and hypothyroidsm, one with ulcerative colitis, and one with myasthenia gravis [74]. In direct correspondence with one of the authors, she confirmed that a number of viscerotropic diseases have occurred in persons with autoimmune diseases. However, it could not be clarified whether these patients were on immunosuppressive or immunomodulatory therapy at the time of YFV. Thus, it remains unclear how to interpret this information. The safety monitoring board in Switzerland has not detected a severe infection with a vaccine strain in an immunosuppressed patient between 2001 and May 2016 [personal communication].

Infections through vaccine strains were extremely rare. However, two of them were deadly. One occurred in a patient with RA/SLE overlap who received YFV four days prior to commencement of MTX/dexamethasone treatment. However, the administered vaccine lot was associated with a 20 times higher risk of YEL-AVD compared to other YFV lots. A fatal disseminated BCG infection was reported upon vaccination of a three-month-old infant born to a mother under IFX treatment. Thus, infants born to immunosuppressed mothers should be vaccinated with caution. The other vaccine-associated infections were either self-limiting or resolved upon treatment.

Regarding reactivation of the underlying disease, apart from one article, no increase of flares of underlying autoimmune conditions was encountered. One study detected a more than 12 times elevated risk of MS exacerbation after YFV [29]. However, this self-controlled case series study was criticized for methodological issues [75].

In SOT patients, one liver transplant rejection was reported three weeks after measles vaccination [37]. Acute organ rejections can occur in around 15-25% of liver transplant recipients [76–78]. Thus it is not surprising to see an acute organ rejection three weeks after measles vaccination (one of 271 liver transplant patients who received a live vaccine), which is most likely only timely but not causally associated to vaccination. Details such as numbers on non-serious specific systemic and local reactions were often not presented in the publications.

Immunogenicity data are difficult to interpret as a large variety of serological and cellular test methods were used. YF (re)vaccinations appeared to be immunogenic in most patient groups. TNFi and MTX therapy seemed to reduce immune responses after VV and HZ vaccination. This is in line with studies on inactivated vaccines, such as pneumococcal and hepatitis A vaccine [79,80]. Rubella vaccinations appeared more immunogenic than measles and mumps vaccination, which is also known in non-immunosuppressed individuals [73]. For VV, one vaccine did often not suffice, but two or more vaccine doses generally conferred satisfactory immunity.

Most studies included in this systematic review were conducted in a non-randomized, uncontrolled and unblinded way and thus are prone to bias. Only eight of 64 included studies were RCTs. Only in one study blinding of patients and study personnel was performed. However, as literature is generally scarce on live vaccines in the immunosuppressed we included observational studies and case reports as our aim was to compile all available evidence on live vaccinations in immunosuppressed IMID, SOT patients as well as BMT patients who received a live vaccine less than two years after transplantation. Furthermore, this systematic review may have missed published studies as the search was conducted in English. Even though we included grey literature, publication bias may have limited the identifiable studies/case reports.

A YEL-AVD occurs in an estimated 0.4 of 100,000 administered vaccine doses [81]. In our identified studies and case reports we found one YEL-AVD in a RA/SLE patient who was vaccinated with a specific vaccine strain associated with a higher YEL-AVD risk. It is well possible that more YEL-AVDs were simply missed/or have not occurred as patient numbers who received a live vaccine are extremely low. Severe reactions or infections may only be discovered if a large number of patients with these conditions receive live vaccines.

Conclusion

Overall, the identified data on live vaccinations in IMID and SOT patients on immunosuppressive treatment as well as patients less than two years after BMT are not sufficiently robust to change the currently available international vaccination recommendations which generally are very restrictive on live vaccines under immunosuppression or shortly after BMT. Only eight randomized controlled trials could be identified and all were conducted in IMID patients. However, patient groups, medications, medication dosages and live vaccinations were diverse within these eight trials and generally patient numbers were low.

From the available evidence we cannot conclude that live vaccines are safe altogether in immunosuppressed IMID, SOT and when administered within two years after BMT. However, despite the limitations discussed above it is re-assuring that in the examined patient groups serious side effects or infections by the attenuated vaccine strain were extremely scarce after primary vaccinations and revaccinations with the examined vaccines (MMR, YFV, VV, HZV, oral typhoid fever, oral polio, BCG, smallpox).

We believe that our research of the existing literature is of help to the interested specialist confronted with the decision process on whether to vaccinate an immunosuppressed patient. More evidence regarding the safety and immunogenicity of live vaccinations in IMID and SOT patients under various immunosuppressive therapies as well as in patients less than two years after BMT is urgently needed. Vaccination recommendations need to be adapted on a regular basis, as more scientific data regarding vaccination safety and efficacy, new vaccines as well as new immunosuppressive therapies will become available.

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Conflic of Interest

None

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Authorship

All authors have made substantial contributions to the conception of the systematic review including serach term definition. SB and VKJ performed eligibility assessment of articles based on titles, key words, and abstracts independently. EC conducted the eligibility assessment based on the full article; this was checked by SB and VKJ. EC performed the data extraction, which was checked by SB and VKJ. All authors have made substantial contributions in the interpretation of the extracted data, drafting of the systematic review and revising it critically for important intellectual content. All authors have approved the final version before submission.

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